C4 wherein each q is independently 0, 1, 2 or 3;

or a pharmaceutically acceptable salt thereof.--

Applicants submit herewith a Marked-Up Version of Amendments showing the changes made attached hereto as **Exhibit A**.

REMARKS

Claims 1, 3-4, 7-8, 10-14, 21-22, 24-25 and 27-28 were pending in the subject application. Claims 8 and 13 were withdrawn from consideration. By this Amendment, applicants have amended claims 1, 3, 4, 22 and 25. Accordingly, upon entry of this Amendment, claims 1, 3, 4, 22 and 25, as amended, and claims 7, 10-12, 14, 21, 24 and 27-28 will be pending and under examination.

Applicants maintain that the amendments to claims 1, 3, 4, 22 and 25 do not raise any issue of new matter. Support for amended claim 1 may be found inter alia in the specification, as originally filed, at page 13, line 2 through page 14, line 22. Support for amended claims 3 and 4 may be found inter alia in the specification, as originally filed, at page 16, lines 1-10. Support for amended claim 22 may be found inter alia in the specification, as originally filed, at page 25, line 20 through page 27, line 3. Support for amended claim 25 may be found inter alia in the specification, as originally filed, at page 29, line 1 through page 30, line 22.

Rejection under 35 U.S.C. §112

On page 3 of the Office Action, the Examiner rejected claims 1, 3, 4, 7, 10-12, 21-22 and 24-25 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner gave the following two reasons that apply and said that any claim not specifically rejected is rejected as being dependent on a rejected claim.

Claims 1, 22 and 25 recite the term "each" in R7 definition which indefinite as there is only one R7 group in the compound of formula I. The Examiner suggested its deletion.

In response, in order to advance the prosecution of the subject application, applicants have amended claims 1, 22 and 25 to delete but without conceding the correctness of the examiner's position the term "each" from the definition of R7. Applicants maintain that by deleting "each" from claims 1, 22 and 25, these claims particularly point out and distinctly claim the subject matter in the instant invention. Accordingly, applicants respectively request that the Examiner reconsider and withdraw this ground of rejection.

On page 3 of the Office Action, the Examiner alleged that the recitation of the term "comprises" in claims 3 and 4 renders these claims indefinite because the transitional phrase "comprises" is open-ended and can include more than what is being

positively recited therein. Furthermore, the Examiner alleged that claims 3 and 4 recite the limitation enantiomers in line 2 and alleged that there is insufficient antecedent basis for this limitation on claim 1 in which claims 3 and 4 are dependent.

In response, in order to advance the prosecution of the subject application, applicants have amended claims 3 and 4 to replace but without conceding the correctness of the examiner's position the term 'comprises' with 'is'. Applicants maintain that by amending claims 3 and 4, these claims particularly point out and distinctly claim the subject matter in the instant invention. Applicants further maintain that there is sufficient antecedent basis for the amendment and direct the Examiner's attention to the specification, as originally filed, on page 16, lines 1-10 that recites "The invention further provides for the (+) or (-) enantiomer of any of the compounds described herein such as a cis isomer or trans isomer." Applicants maintain that this phrase expressly provides the sufficient antecedent basis for this limitation on claim 1 in which claims 3 and 4 are dependent. Accordingly, applicants respectively request that the Examiner reconsider and withdraw this ground of rejection.

Claim Rejections: 35 U.S.C. §102/103 - Chapelo, et al.

On page 4 of the Office Action the Examiner rejected claims 1, 7, 21-22 and 24-25 under 35 U.S.C. §102(b) as being anticipated by Chapelo et al., J. Med. Chem. 33, 1627-1630, 1989. The Examiner alleged that Chapelo et al. teaches heteroaromatic analogues of the 2 adrenergic receptor agonist clonidine, which includes

compounds claimed herein. The Examiner cited compounds 15 and 16 shown on scheme 1 page 1627, on Table 1, treating data on Table II on page 1628, experimental details on page 1630 for making these compounds.

In response, but without conceding the correctness of the Examiner, applicants have amended claims 1, 22 and 25 to limit m = 1 or 2 thereby excluding the compounds of Chapelo, et al., i.e. where the 2-imidazolinylamino group branches off the 6-position of the indole skeleton. Applicants maintain that as to amended claims 1, 22 and 25, this ground of rejection is no longer applicable and request that it be reconsidered and withdraw.

On page 6 of the Office Action, the Examiner rejected claims 27 and 28 under 35 U.S.C. §103(a). The Examiner alleged that while compounds 15 and 16 do not anticipate the scope of claims 27 and 28 they are very closely related, being positional isomers of indole compounds, i.e. 2-imidazolinylamino group in the 4 position the phenyl ring as opposed to 2-imidazolinylamino group in the 3 position to the phenyl ring. The Examiner cited In re Crounse, 150 USPQ 554; In re Norris 84 USPQ 458; In re Finely 81 USPQ 383 and 387; Ex parte Englehardt, 208 USPQ 343; Ex parte Henkel, 130 USPQ 474, regarding positional isomers. The Examiner then alleged that it would have been obvious to one skilled in the art at the time of the invention was made would be motivated to make these positional isomeric compounds as he would expect these compounds to possess the utility taught by the applied art in view of the close structural similarity outlined above.

In response, applicants maintain that compounds 15 and 16 of the Chapelo, et al. do not anticipate the subject matter in claims 1, 22 and 25, as amended. Applicants direct the Examiner's attention to page 1627, second column, that recites "indolines 15 and 16 proved to be of no interest...there was an indication that the 'B' position was the favored position of attachment for the aminoimidazoline moiety when considering 2-agonist activity." Chapelo teaches that the "B" position is the desired position of the aminoimidazoline moiety. Since Chapelo teaches that compounds of 15 and 16 with the aminoimidazoline moiety at the "A" position would lead to reduced 2-agonist activity, applicants maintain that the compounds of Chapelo et al. do not suggest or render obvious applicants' compounds of claims 27 and 28. Accordingly, applicants respectively request that the Examiner reconsider and withdraw this ground of rejection.

Claim Rejections: 35 U.S.C. §102/103 - Henry, et al.

On page 5 of the Office Action, the Examiner rejected claims 1, 3-4, 7, 11-12, 14, 21-22 and 24-25 under 35 U.S.C. §102(e) as being anticipated by Henry et al., United States Patent No. 6,162,818, issued on December 19, 2000. The Examiner alleged that Henry et al. teaches several 2-imidazolinylaminoindole compounds useful as 2-adrenoreceptor agonists for treating various disorders of the 2-adrenoreceptors, which include the compounds claimed in the instant claims. The Examiner directed attention to the formula 1 on column 3 and noted the definitions of R1, R2, R3, R4, R5, R6 and R7. The Examiner noted that R1 is mislabeled as R8; both the abstract and the tables that disclose the compounds support this correction. The Examiner further pointed

out that R4, R5 and R6 can be a 2-imidazolinylamino group. The Examiner directed applicant's attention to examples 193-250, 251-310, and 377-438 on column 25 through 29, which includes compounds claimed in the instant claims for the same use.

On page 6 of the Office Action, the Examiner rejected claims 27 and 28 under 35 U.S.C. 103(a) as being unpatentable over Henry, et al., United States Patent No. 6,162,818, issued on December 19, 2000. The Examiner incorporated the alleged teachings of Henry, et al. as discuss in the above 102 rejection. The Examiner further alleged that while Henry compounds don't anticipate the scope of claims 27 and 28, they are very closely related, being positional isomers of indole compounds i.e. -imidazolinylamino group in the 4 position the phenyl ring as opposed to 2-imidazolinylamino group in the 3 position to the phenyl ring. The Examiner cited In re Crounse, 150 USPQ 554; In re Norris 84 USPQ 458; In re Finely 81 USPQ 383 and 387; Ex parte Englehardt, 208 USPQ 343; Ex parte Henkel, 130 USPQ 474, regarding positional isomers. The Examiner then alleged that it would have been obvious to one skilled in the art at the time of the invention was made would be motivated to make these positional isomeric compounds as he would expect these compounds to possess the utility taught by the applied art in view of the close structural similarity outlined above.

In response, applicants respectfully traverse the rejection under 35 U.S.C. §102(e) and maintain that the pending claims are patentable over Henry et al., United States Patent No. 6,162,818, issued December 19, 2000.

Applicants note that Henry, et al., United States Patent No. 6,162,818, issued on December 19, 2000 as a continuation of PCT International Application No. PCT/US97/20801, filed November 21, 1997, which claims priority of U.S. Provisional Application No. 60/031,777, filed November 11, 1996. Accordingly, the earliest possible effective date of Henry, et al. as a reference is November 11, 1996 (Applicants do not concede that Henry, et al. is in fact, entitled to a November 11, 1996 effective filing date). Applicants will shortly submit a Declaration Under 37 C.F.R. § 1.131 establishing a date of invention for the subject matter of the invention as now claimed prior to November 11, 1996.

Accordingly, in view of the preceding remarks and the Declaration to be submitted, applicants respectively request that the Examiner reconsider and withdraw Henry, et al. as a reference and all rejections based thereon.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone the number provided.

No fee, other than the enclosed fee of $465.00 for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

John P. White
Registration No. 28,678
Attorney for Applicants
Cooper & Dunham LLP
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New York, New York 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231

2/10/03

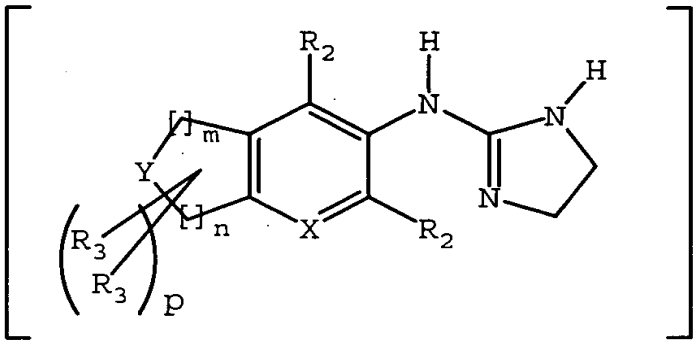
John P. White
Reg. No. 28,678

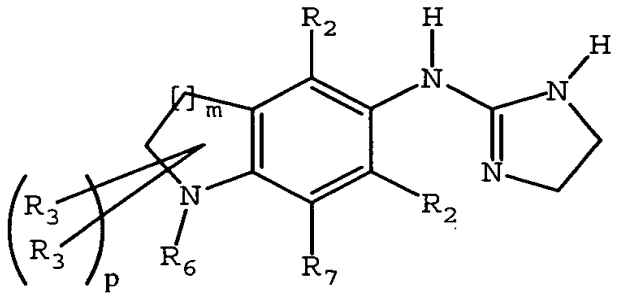
Date

Marked-Up Version of Amendments

Additions to the text are indicated by underlining; deletions are indicated by square brackets.

1.(Twice Amended) A compound having the structure:





[wherein X is CR_7;]

[wherein Y is O; S; or NR_6;]

wherein each R_2 is independently H; F; Cl; Br; I; $-NO_2$, -CN; straight chained or branched C_1-C_4 alkyl; C_1-C_4 monofluoroalkyl or C_1-C_4 polyfluoroalkyl; straight chained or branched C_1-C_4 alkoxy; -OH; $-(CH_2)_qOH$; $-COR_4$; CO_2R_4; $CONHR_4$; phenyl; or benzyl;

wherein each R_3 is independently H; straight chained or branched C_1-C_4 alkyl; C_1-C_4 monofluoroalkyl or C_1-C_4 polyfluoroalkyl; straight chained or branched C_1-C_4 alkoxy; $-(CH_2)_qOH$; -OH; $=N-OR_4$; COR_4; CO_2R_4; $CONHR_4$; phenyl; or benzyl;

wherein each R_4 is independently H; straight chained or branched C_1-C_4 alkyl, C_1-C_4 monofluoroalkyl or C_1-C_4 polyfluoroalkyl; or phenyl;

wherein R_6 is H; straight chained or branched C_1-C_4 alkyl; C_1-C_4 monofluoroalkyl or C_1-C_4 polyfluoroalkyl; straight chained or branched C_1-C_4 alkoxy; $-CH_2CH_2(CH_2)_qOH$; COR_4; CO_2R_4; $CONHR_4$; phenyl; or benzyl;

wherein each R_7 is independently H; -CN; straight chained or branched C_1-C_4 alkyl; C_1-C_4 monofluoroalkyl or C_1-C_4 polyfluoroalkyl; straight chained or branched C_1-C_4 alkoxy; -OH; $-(CH_2)_qOH$; $-COR_4$; CO_2R_4; $CONHR_4$; phenyl; or benzyl;

wherein m is 1 or 2 [wherein m and n are each independently 0, 1, 2 or 3, provided that m+n is 2 or 3];

wherein each p is independently 0, 1 or 2; and

wherein each q is independently 0, 1, 2 or 3;

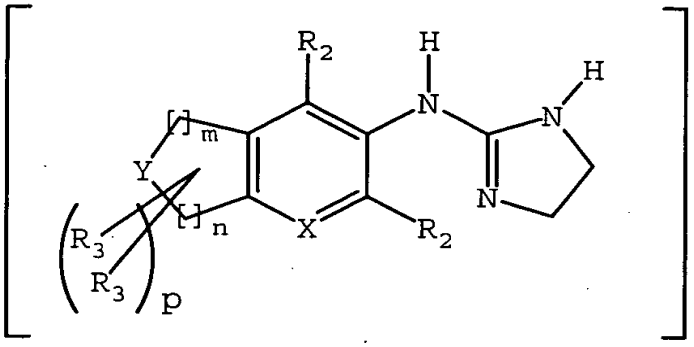
or a pharmaceutically acceptable salt thereof.--

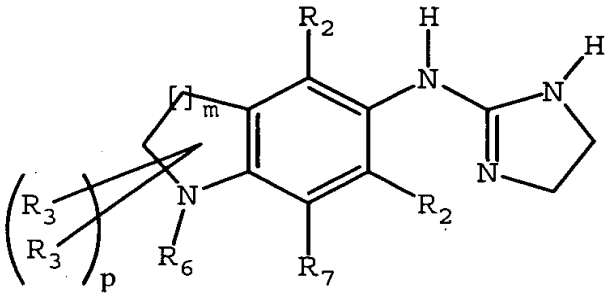
--3. (Twice Amended) The compound of claim 1, wherein the compound [comprises] is the (+) enantiomer.--

--4. (Twice Amended) The compound of claim 1, wherein the

compound [comprises] is the (-) enantiomer.--

--22. (Amended) A method for treating an α_2 adrenergic receptor associated disorder in a subject, which comprises administering to the subject an amount of a compound effective to treat the disorder, wherein the compound has the structure:





[wherein X is CR_7;]

[wherein Y is O; S; or NR_6;]

wherein each R_2 is independently H; F; Cl; Br; I; $-NO_2$, -CN; straight chained or branched C_1-C_4 alkyl; C_1-C_4 monofluoroalkyl or C_1-C_4 polyfluoroalkyl; straight chained or branched C_1-C_4 alkoxy; -OH; $-(CH_2)_qOH$; $-COR_4$; CO_2R_4; $CONHR_4$; phenyl; or benzyl;

wherein each R_3 is independently H; straight chained or branched C_1-C_4 alkyl; C_1-C_4 monofluoroalkyl or C_1-C_4 polyfluoroalkyl; straight chained or branched C_1-C_4 alkoxy; $-(CH_2)_qOH$; -OH; $=N-OR_4$; COR_4; CO_2R_4; $CONHR_4$; phenyl; or benzyl;

wherein each R_4 is independently H; straight chained or branched C_1-C_4 alkyl, C_1-C_4 monofluoroalkyl or C_1-C_4 polyfluoroalkyl; or phenyl;

wherein R_6 is H; straight chained or branched C_1-C_4 alkyl; C_1-C_4 monofluoroalkyl or C_1-C_4 polyfluoroalkyl; straight chained or branched C_1-C_4 alkoxy; $-CH_2CH_2(CH_2)_qOH$; COR_4; CO_2R_4; $CONHR_4$; phenyl; or benzyl;

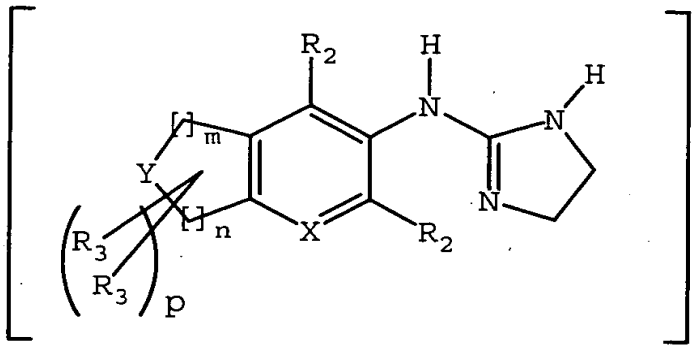
wherein each R_7 is independently H; -CN; straight chained or branched C_1-C_4 alkyl; C_1-C_4 monofluoroalkyl or C_1-C_4 polyfluoroalkyl; straight chained or branched C_1-C_4 alkoxy; -OH; $-(CH_2)_qOH$; $-COR_4$; CO_2R_4; $CONHR_4$; phenyl; or benzyl;

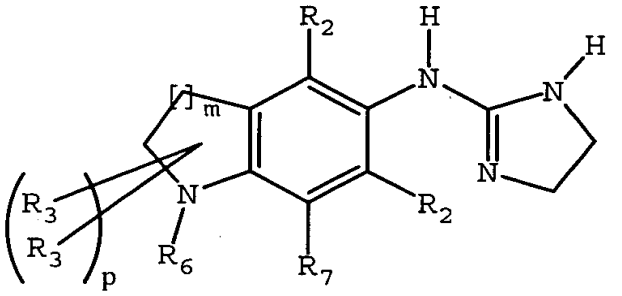
wherein m is 1 or 2 [wherein m and n are each independently 0, 1, 2 or 3, provided that m+n is 2 or 3];

wherein each p is independently 0, 1 or 2; and

wherein each q is independently 0, 1, 2 or 3.--

--25. (Amended) A method of treating pain in a subject, which comprises administering to the subject an amount of a compound effective to treat the subject's pain, wherein the compound has the structure:





[wherein X is CR_7;]

[wherein Y is O; S; or NR_6;]

wherein each R_2 is independently H; F; Cl; Br; I; $-NO_2$, -CN; straight chained or branched C_1-C_4 alkyl; C_1-C_4 monofluoroalkyl or C_1-C_4 polyfluoroalkyl; straight chained or branched C_1-C_4 alkoxy; -OH; $-(CH_2)_qOH$; $-COR_4$; CO_2R_4; $CONHR_4$; phenyl; or benzyl;

wherein each R_3 is independently H; straight chained or branched C_1-C_4 alkyl; C_1-C_4 monofluoroalkyl or C_1-C_4 polyfluoroalkyl; straight chained or branched C_1-C_4 alkoxy; $-(CH_2)_qOH$; -OH; $=N-OR_4$; COR_4; CO_2R_4; $CONHR_4$; phenyl; or benzyl;

wherein each R_4 is independently H; straight chained or branched C_1-C_4 alkyl, C_1-C_4 monofluoroalkyl or C_1-C_4 polyfluoroalkyl; or phenyl;

wherein R_6 is H; straight chained or branched C_1-C_4 alkyl; C_1-C_4 monofluoroalkyl or C_1-C_4 polyfluoroalkyl; straight chained or branched C_1-C_4 alkoxy; $-CH_2CH_2(CH_2)_qOH$; COR_4; CO_2R_4; $CONHR_4$; phenyl; or benzyl;

wherein each R_7 is independently H; -CN; straight chained or branched C_1-C_4 alkyl; C_1-C_4 monofluoroalkyl or C_1-C_4 polyfluoroalkyl; straight chained or branched C_1-C_4 alkoxy; -OH; $-(CH_2)_qOH$; $-COR_4$; CO_2R_4; $CONHR_4$; phenyl; or benzyl;

wherein m is 1 or 2 [wherein m and n are each independently 0, 1, 2 or 3, provided that m+n is 2 or 3];

wherein each p is independently 0, 1 or 2; and

wherein each q is independently 0, 1, 2 or 3.--